REMARKS

Claims 1-43 are pending. Claims 1-40 stand rejected in the present application. Claims 41-43 are withdrawn as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Rejections under 35 U.S.C. §112, first paragraph.

Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention. The Office Action states that the "specification, while being enabled for compounds of formula II, does not reasonably provide enablement for all other compounds embraced by the instant claims." The Office Action also asserts that the "specification fails to enable the preparation of the compounds that are used in the instantly claimed inhibitory method." Applicants respectfully traverse this rejection.

Applicants respectfully point out that the invention would not be enabled only if a skilled artisan would require undue experimentation to practice the invention. Applicants direct the Examiner's attention to MPEP 2164.04, which delineates the burden carried by the PTO in order to make a *prima facie* case of lack of enablement. The provision states that the Examiner must "establish a reasonable basis to question the enablement provided for the claimed invention," and that "it is incumbent upon the Patent Office, whenever making a rejection on this basis, "to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning...." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). Moreover, the Examiner must consider the level of skill in the art. As set forth in MPEP §2164.06, "a considerable amount of experimentation is permissible, if it is merely routine," such that, as stated in MPEP 2164.01(c), "if the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied."

The arguments set forth in the Office Action do not satisfy the PTO's burden. The arguments fail to provide a reasonable basis for the rejections and, indeed, they vitiate entirely the level of skill accorded to one of skill in the art.

The Office Action asserts that Applicants have failed to provide guidance on the preparation of suitable compounds other than the "quinazoline compounds." However, Applicants respectfully point out that the application provides guidance as to a variety of suitable compounds both among and in addition to the referenced "quinazoline compounds." The specification discloses over 50 exemplary compounds in Figure 32a-32m, each having differences in chemical structure. The listed compounds differ widely, and include at least three distinct classes of compounds. See, for example, compounds 32-35, 47-49, and 77-82. Thus, compounds other than the "quinazoline compounds" are clearly both disclosed and enabled by the specification.

Furthermore, Applicants submit that, as of the priority date of this application, one skilled in the art would readily have been able to identify additional compounds within the scope of those recited in the claims through use of chemical libraries. The application teaches the use of chemical libraries for the identification of lead compounds, as discussed for example on pp. 87-92. To illustrate, Applicants themselves used commercially available compound libraries to identify the compounds depicted in Figure 32, as shown in the specification on pp. 92-94. Although the specification may not provide extensive guidance on the procurement of chemical libraries, MPEP 2164.05(a) makes clear that the "specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*." Chemical libraries, each with thousands of different compounds, were not only readily prepared but were commercially available before this application was filed, and those skilled in the art would readily have been able to procure and test such libraries in the assays described in the specification, e.g., on pages 90-92. Those compounds described in the specification on pp. 87-95 are merely illustrative, and "widely diverse libraries of compounds" can be synthesized or procured and used. See p. 90.

To support this position, Applicants submit herewith Exhibit A, a copy of *Drug & Market Development*, 1998, Vol. 9, 89-104, showing that, well before the filing of this application, high

through-put screening techniques were used to screen thousands of individual compounds and other materials for effectiveness in processes of interest. Similarly, Applicants submit as Exhibit B a copy of Arenas et al., *Nucleic Acids Symposium Series*, 1999, No. 41, 13-16, to show that a skilled artisan would have been able to screen libraries of thousands of compounds derived from a variety of different chemical classes. Id. at 15.

Thus, one skilled in the art would readily have been able to apply well-known screening techniques to chemical libraries and identify exemplary active compounds of widely varying structures in the disclosed assays. For example, Applicants point to the available screening assays disclosed on pp. 90-92 of the specification. No undue experimentation would have been required to apply these assays to high-throughput screening techniques; indeed the practice was routine, if not trivial. Accordingly, Applicants respectfully request the withdrawal of the enablement rejection.

The Office Action's assertion that inadequate correlation is shown between the "*in vitro* data" and "*in vivo* applications" is misplaced. As discussed in MPEP §2164.02, either an *in vitro* or *in vivo* example provides an adequate working example to enable a claimed method if the example correlates with the method. Applicants have claimed a method of inhibiting a hedgehog pathway in a cell having a functional *patched* receptor. The described experiments clearly exemplify this method, including those seen on pp. 92-95 of the specification. The method can easily be applied to cell culture development. For example, p. 48 illustrates the use a *hedgehog* antagonist to alter the rate of proliferation of neuronal stem cells in a cell culture, which may assist in generating and/or maintaining arrays of different vertebrate tissue.

Applicants also respectfully assert that the reference to Bale et al. is inapposite to Applicants' claims. As exemplified on p. 94 of the specification, Applicants' claimed method includes the use of a compound that inhibits the hedgehog pathway in a cell having a functional patched receptor but does not inhibit the hedgehog pathway in a *patched*-null cell, i.e., a cell that lacks a functional patched receptor. To the extent the Bale article refers to mutated cells having no functional patched receptor, Applicants' claimed method would not be expected to inhibit the hedgehog pathway, and thus the existence or not of known correlations between various observed phenotypes and the "nature or location of mutations" is irrelevant. On the other hand,

the claimed method is applicable to a variety of physiological systems having no patched mutations. For example, the method is applicable not only to cell culture, as mentioned above, but also to the control of hair growth (pp. 65-66) and to spermatogenesis (p. 66), all of are relevant to cells with functional patched receptors.

If the Examiner wishes to maintain the rejection, in light of Applicants' arguments of record and the presumption in favor of Applicants, it is respectfully asserted that the present rejection must be supported by substantial evidence to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). No art has been made of record other than Bale et al., which is clearly inapposite to Applicants' claimed invention as argued above. Nor has the Examiner relied on any other fact-finding results to rebut the presumption in favor of Applicants or to support the argument that one skilled in the art would have required undue experimentation to make and use the claimed invention. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections based on 35 U.S.C. 112, second paragraph.

Claims 1-40 are also rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

As discussed in MPEP §2171, the relevant inquiry under 35 U.S.C. 112, second paragraph, is whether the scope of the claim is clear to one skilled in the art. Applicants note that the Office Action provides reasons for rejection only with respect to claims 12 and 30, and that accordingly no other claims are subject to the indefiniteness rejection.

Regarding claim 12, the Office Action requests that the Applicants clarify the phrase "normal cell." Applicants submit that one of skill in the art would recognize that, as the term is used in the pending claims, a "normal cell" is a cell that has a functional *patched* receptor, e.g., does not have a *patched*-null mutation. In contrast, a *patched*-null cell is a cell in which the hedgehog pathway is constitutively active, that is, the hedgehog pathway is active whether or not hedgehog itself is present to stimulate activity in the pathway. Thus, *patched* down-regulates the

hedgehog pathway in a "normal cell" but not in a *patched*-null cell, as shown, for example, on p. 95 of the specification where jervine, a known patched pathway antagonist, significantly decreased the expression of *gli*-1 mRNA in *ptc*-null cells. Applicants have amended the claims to state this definition explicitly, and submit that the amendment does not narrow the scope of the claims but merely recites the meaning of "normal cell" as it would have been understood by one skilled in the art in the context of the claims and the specification of the instant application.

As to any other reason claim 12 is alleged to be indefinite, Applicants note that the MPEP provides that mere breadth does not result in indefiniteness. MPEP 2173.04. Applicants submit that one skilled in the art will readily understand the scope of the claim, however broad it may be. Claim 12 refers to the method of claim 2, wherein the compound causes a decrease in *gli* transcription of at least about 10% relative to an untreated control cell. Claim 2 refers to the method of claim 1, wherein the compound has a molecular weight less than about 2000 amu. Claim 1 refers to a method of inhibiting a *hedgehog* pathway in a cell having a functional *patched* receptor, comprising administering an effective amount of a compound that inhibits the hedgehog pathway in a cell having a functional *patched* receptor but does not inhibit the *hedgehog* pathway in a *patched*-null cell. Each of these claims clearly identifies the properties of the referenced compounds – both as to what the compounds do and do not do. Applicants therefore submit that one skilled in the art would have understood the metes and bounds of each of these claims, both separately and together. Applicants respectfully request clarification of the grounds of rejection to the extent the rejection is maintained on this basis.

Regarding claim 30, Applicants note that the compound shown in the structural formula represents a hedgehog agonist, a compound that activates the hedgehog pathway. As discussed in the specification on pp. 11-12, certain compounds inhibit activation of the hedgehog pathway by hedgehog protein but do not inhibit activation of the pathway by this particular agonist. Although one skilled in the art would have understood the scope of claim 30 without this amendment, Applicants have amended claim 30 to make explicit that the compound inhibits activation of the hedgehog pathway by hedgehog protein, but does not inhibit activation of the hedgehog pathway by the recited hedgehog agonist.

For the reasons stated above, Applicants submit that the claims fully comply with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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